comparable to those obtained in open-label studies as well as those of blinded trials.

Our trial included more patients with cardioembolic stroke than other studies, probably because of the exclusion of those of mild severity (NIHSS ≤4). It has been reported that more than half of patients with lacunar stroke exhibit mild deficits with an NIHSS score ≤4.[2] Moreover, cardioembolic strokes generally arrive at hospital much earlier than other subtypes,[2] which could influence the distribution of stroke subtypes. In any event, the present high proportion of cardioembolic stroke is unlikely to favor the present trial because stroke subtype is not associated with outcome of thrombolysis when adjusted for severity.[35,36] Comparisons of data from different countries, with different medical, social, and racial backgrounds, should be interpreted cautiously. Nontreated historical controls were available in a Japanese stroke registration study[37] involving 312 ischemic stroke patients referred to hospital within 3 hours after onset and not receiving any thrombolytic therapy. The mean age was 73.5 years, the median NIHSS score was 12, and the proportion of mRS score of 0 to 1 at 3 months was 21%. This proportion is 16% lower than that of the Japan Alteplase Clinical Trial, whereas the backgrounds were comparable.

In our trial, apart from sICH, asymptomatic ICH was detected in 17% on initial 36-hour CT, exceeding that reported in the NINDS trial (5%). Under the careful and stringent panel reading in our study, all questionable hyperintensity was adjudged to involve hemorrhage. The incidence of asymptomatic ICH was 31% in the initial 10 days of treatment, which was comparable to the 40% in the initial 7 days of the ECASS-II trial.[6]

In conclusion, 0.6 mg/kg intravenous alteplase in Japanese patients with acute ischemic stroke is likely comparable to data reported for patients in North America and the EU at a 0.9 mg/kg dose. Further studies are needed to confirm these results.

Appendix

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Disclosures

None.

References

1. The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. *N Engl J Med.* 1995;333:1581–1587.
2. Kimura K, Kazui S, Minematsu K, Yamaguchi T; for the Japan Multicenter Stroke Investigators' Collaboration (J-MUSIC). Analysis of 16 922 patients with acute ischemic stroke and transient ischemic attack in Japan. *Cerebrovasc Dis.* 2004;18:47–56.
3. Mori E, Yoneda Y, Tabuchi M, Yoshida T, Ohkawa S, Ohsumi Y, Kitano K, Tsutsumi A, Yamadori A. Intravenous recombinant tissue plasminogen activator in acute carotid artery territory stroke. *Neurology.* 1992;42:976–982.
4. Yamaguchi T, Hayakawa T, Kikuchi H; Japanese Thrombolysis Study Group. Intravenous tissue plasminogen activator ameliorates the outcome of hyperacute embolic stroke. *Cerebrovasc Dis.* 1993;3:269–272.
5. Yamaguchi T, Kikuchi H, Hayakawa T; Japanese Thrombolysis Study Group. Clinical efficacy and safety of intravenous tissue plasminogen activator in acute embolic stroke: a randomized, double-blind, dose-comparison study of duteplase. In Yamaguchi T, Mori E, Minematsu K, del Zoppo GJ, eds. *Thrombolytic Therapy in Acute Ischemic Stroke III*. Tokyo, Japan: Springer-Verlag; 1995:223–229.
6. Hacke W, Kaste M, Fieschi C, von Kummer R, Davalos A, Meier D, Larrue V, Bluhmki E, Davis S, Donnan G, Schneider D, Diez-Tejedor E, Trouillas P. Randomised double-blind placebo-controlled trial of thrombolytic therapy with intravenous alteplase in acute ischaemic stroke (ECASS II). *Lancet.* 1998;352:1245–1251.
7. Grond M, Stenzel C, Schmulling S, Rudolf J, Neveling M, Lechleuthner A, Schneweis S, Heiss WD. Early intravenous thrombolysis for acute ischemic stroke in a community-based approach. *Stroke.* 1998;29:1544–1549.
8. Tanne D, Bates VE, Verro P, Kasner SE, Binder JR, Patel SC, Mansbach HH, Daley S, Schultz LR, Karanjia PN, Scott P, Dayno JM, Vereczkey-Porter K, Benesch C, Book D, Coplin WM, Dulli D, Levine SR; t-PA Stroke Survey Group. Initial clinical experience with IV tissue plasminogen activator for acute ischemic stroke: a multicenter survey. *Neurology.* 1999;53:424–427.
9. Wang DZ, Rose JA, Honings DS, Garwacki DJ, Milbrandt JC. Treating acute stroke patients with intravenous tPA: the OSF Stroke Network experience. *Stroke.* 2000;31:77–81.
10. Albers GW, Bates VE, Clark WM, Bell R, Verro P, Hamilton SA. Intravenous tissue-type plasminogen activator for treatment of acute stroke: the standard treatment with alteplase to reverse stroke (STARS) study. *J Am Med Assoc.* 2000;283:1145–1150.

11. Katzan IL, Furlan AJ, Lloyd LE, Frank JI, Harper DL, Hinchey JA, Hammel JP, Qu A, Sila CA. Use of tissue-type plasminogen activator for acute ischemic stroke: the Cleveland area experience. *J Am Med Assoc.* 2000;283:1151–1158.
12. Barber PA, Demchuk AM, Zhang J, Buchan AM. Validity and reliability of a quantitative computed tomography score in predicting outcome of hyperacute stroke before thrombolytic therapy. *Lancet.* 2000;355: 1670–1674.
13. Schmulling S, Grond M, Rudolf J, Heiss WD. One-year follow-up in acute stroke patients treated with rtPA in clinical routine. *Stroke.* 2000; 31:1552–1554.
14. Lopez-Yunez AM, Bruno A, Williams LS, Yilmaz E, Zurru C, Biller J. Protocol violations in community-based rTPA stroke treatment are associated with symptomatic intracerebral hemorrhage. *Stroke.* 2001;32: 12–16.
15. Bath P. Alteplase not yet proven for acute ischaemic stroke. *Lancet.* 1998;352:1238–1239.
16. Marler JR, Tilley BC, Lu M, Brott TG, Lyden PC, Grotta JC, Broderick JP, Levine SR, Frankel MP, Horowitz SH, Haley EC Jr, Lewandowski CA, Kwiatkowski TP; NINDS rt-PA Stroke Study Group. Early stroke treatment associated with better outcome. *Neurology.* 2000;55: 1649–1655.
17. Uchino K, Alexandrov AV, Garami Z, El-Mitwalli A, Morgenstern LB, Grotta JC. Safety and feasibility of a lower dose intravenous tPA therapy for ischemic stroke beyond the first three hours. *Cerebrovasc Dis.* 2005; 19:260–266.
18. Brott TG, Haley EC Jr, Levy DE, Barsan W, Broderick J, Sheppard GL, Spilker J, Kongable GL, Massey S, Reed R, Marler JR. Urgent therapy for stroke: part I. Pilot study of tissue plasminogen activator administered within 90 minutes. *Stroke.* 1992;23:632–640.
19. Haley EC Jr, Levy DE, Brott TG, Sheppard GL, Wong MCW, Kongable GL, Torner JC, Marler JR. Urgent therapy for stroke: part II. Pilot study of tissue plasminogen activator administered 91–180 minutes from onset. *Stroke.* 1992;23:641–645.
20. Ueshima S, Matsuo O. The differences in thrombolytic effects of administrated recombinant t-PA between Japanese and Caucasians. *Thromb Haemost.* 2002;87:544–546.
21. Sane DC, Stump DC, Topol EJ, Sigmon KN, Clair WK, Kereiakes DJ, George BS, Stoddard MF, Bates ER, Stack RS, Califf RM; Thrombolysis and Angioplasty in Myocardial Infarction Study Group. Racial differences in responses to thrombolytic therapy with recombinant tissue-type plasminogen activator: increased fibrin(ogen)olysis in blacks. *Circulation.* 1991;83:170–175.
22. del Zoppo GJ, Poeck K, Pessin MS, Wolpert SM, Furlan AJ, Ferbert A, Alberts MJ, Zivin JA, Wechsler L, Busse O, Greenlee R Jr, Brass L, Mohr JP, Feldmann E, Hacke W, Kase CS, Biller J, Gress D, Otis SM. Recombinant tissue plasminogen activator in acute thrombotic and embolic stroke. *Ann Neurol.* 1992;32:78–86.
23. Temple R. Policy developments in regulatory approval. *Stat Med.* 2002; 21:2939–2948.
24. Koennecke HC, Nohr R, Leistner S, Marx P. Intravenous tPA for ischemic stroke team performance over time, safety, and efficacy in a single-center, 2-year experience. *Stroke.* 2001;32:1074–1078.
25. Merino JG, Silver B, Wong E, Foell B, Demaerschalk B, Tamayo A, Poncha F, Hachinski V. Extending tissue plasminogen activator use to community and rural stroke patients. *Stroke.* 2002;33:141–146.
26. Davalos A, Alvarez-Sabin J, Marti-Vilalta JL, Castillo J. Tratamiento intravenoso con activador del plasminogeno tisular en la isquemia cerebral aguda. *Med Clin (Barc).* 2003;120:1–5.
27. Labiche LA, Al-Senani F, Wojner AW, Grotta JC, Malkoff M, Alexandrov AV. Is the benefit of early recanalization sustained at 3 months? A prospective cohort study. *Stroke.* 2003;34:695–698.
28. Schenkel J, Weimar C, Knoll T, Haberl RL, Busse O, Hamann GF, Koennecke HC, Diener HC. R1-systemic thrombolysis in German stroke units: The experience from the German Stroke data bank. *J Neurol.* 2003;250:320–324.
29. Lindsberg PJ, Soinne L, Roine RO, Salonen O, Tatlisumak T, Kallela M, Happola O, Tiainen M, Haapaniemi E, Kuisma M, Kaste M. Community-based thrombolytic therapy of acute ischemic stroke in Helsinki. *Stroke.* 2003;34:1443–1449.
30. Dubey N, Bakshi R, Wasay M, Dmochowski J. Early computed tomography hypodensity predicts hemorrhage after intravenous tissue plasminogen activator in acute ischemic stroke. *J Neuroimaging.* 2001; 11:184–188.
31. Hill MD, Buchan AM; CASES Investigators. Methodology for the Canadian activase for stroke effectiveness study (CASES). *Can J Neurol Sci.* 2001;28:232–238.
32. Grotta JC, Burgin WS, El-Mitwalli A, Long M, Campbell M, Morgenstern LB, Malkoff M, Alexandrov AV. Intravenous tissue-type plasminogen activator therapy for ischemic stroke: Houston experience 1996 to 2000. *Arch Neurol.* 2001;58:2009–2013.
33. Rymer MM, Thurtchley D, Summers D. Expanded modes of tissue plasminogen activator delivery in a comprehensive stroke center increases regional acute stroke interventions. *Stroke.* 2003;34:e58–e60.
34. Scott PA, Silbergleit R. Misdiagnosis of stroke in tissue plasminogen activator-treated patients: characteristics and outcomes. *Ann Emerg Med.* 2003;42:611–618.
35. The NINDS t-PA Stroke Study Group. Generalized efficacy of t-PA for acute stroke: subgroup analysis of the NINDS t-PA stroke trial. *Stroke.* 1997;28:2119–2125.
36. Hsia AW, Sachdev HS, Tomlinson J, Hamilton SA, Tong DC. Efficacy of IV tissue plasminogen activator in acute stroke: does stroke subtype really matter? *Neurology.* 2003;61:71–75.
37. Kobayashi S, Terasaki T, Hashimoto Y, Inoue I, Nakagawara J, Yamada T, Suzuki A. Three-month outcome of ischemic stroke patients admitted within 3 hours: prospective study using stroke database of Japanese standard stroke registry. *Jpn J Stroke.* 2004;26:323–330 (in Japanese).

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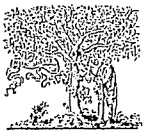

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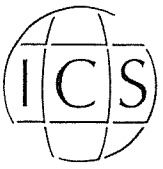

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Recent advances in acute stroke management

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Abstract. In this review, the author discusses mainly the results of the nationwide survey demonstrating the current status of management of patients with acute ischemic stroke, and the history as well as present status of thrombolytic therapy for acute ischemic stroke in Japan. © 2006 Elsevier B.V. All rights reserved.

Keywords: Intracranial hemorrhage; Ischemic penumbra; Randomized controlled trial; Recombinant tissue plasminogen activator; Thrombolysis

1. Introduction

Stroke mortality has decreased dramatically in Japan since the early 1960s. The phenomenon was mainly caused by a decrease in fatal brain hemorrhage. A decrease in the prevalence of hypertension, changes in patterns of lifestyle, and improved antihypertensive therapy are likely to have reduced the incidence and severity of brain hemorrhage and other hypertension-related stroke [1]. However, stroke mortality is still high, approximately 140,000 persons/year, the third leading cause of death, following neoplasm and heart diseases. The number of stroke patients being treated in outpatient clinics or hospitals is estimated to be 1.5 million. Approximately 75% of stroke patients have brain infarction. Stroke patients accounted for 30–40% of care-receivers, taking the first place.

Aged population over 65 years old is rapidly increasing up to 30% of the Japanese population by the year 2025. The number of stroke patients is, therefore, estimated to increase up to 3 million in the years 2020–2025. How can we overcome all difficulties in stroke management?

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2. History of thrombolytic therapy for acute ischemic stroke

The new era has begun for acute stroke therapy since the success of hyperacute thrombolytic therapy in 1995 [2]. The strategy of the therapy is based on the concept that early reperfusion rescues reversibly damaged brain tissues in the ischemic penumbra and promotes the recovery from acute stroke [3–5].

Many clinical studies suggested that treatment with thrombolytic agents can promote recanalization of the occluded cerebral arteries and may result in better neurological recovery in acute ischemic stroke patients if the treatment is initiated very early after the stroke onset [6]. Favourable outcome by hyperacute therapy with a recombinant tissue plasminogen activator (rt-PA), duteplase, was firstly demonstrated by randomized controlled trials (RCTs) carried out here in Japan [7,8]. These observations were finally confirmed by a large-sized RCT ($n=624$), the National Institute of Neurological Disorders and Stroke (NINDS) rt-PA stroke study, in 1995 [2]. In NINDS study, an rt-PA, alteplase, was effective in increasing a complete or near-complete recovery (modified Rankin Scale, mRS, score, 0 or 1) in 3 months, if the agent was injected intravenously within the initial 3 h after stroke onset. Other RCTs using intravenous rt-PA therapy within 6 h or 3 to 5 h after stroke onset that were carried out in Europe or USA could not demonstrate effectiveness and safety [9–11].

The Prolysis in Acute Cerebral Thromboembolism II (PROACT II) trial was the first multicenter RCT in which the efficacy and safety of intra-arterial thrombolysis were evaluated [12]. The therapy using prourokinase (proUK) had a benefit in patients who had a stroke caused by occlusion of the middle cerebral artery (MCA) and were treated within 6 h after symptom onset. This therapy, however, has not yet been approved because of a relatively small number of the studied patients (n=180).

3. Guidelines for the early stroke management

The alteplase treatment within 3 h after stroke onset is now approved for use to ischemic stroke patients in more than 40 countries, including USA, Canada, and many European and Asian countries. Stroke has become a medical emergency and has been called "Brain Attack" since 1996, when the therapy was first approved by the Food and Drug Administration (FDA) in USA.

In most current guidelines of acute stroke management, intravenous alteplase (0.9 mg/kg, maximum dose 90 mg) is strongly recommended for carefully selected patients who can be treated within 3 h of onset of ischemic stroke [13–15]. Thrombolytic therapy, however, may be a double-edged sword for and against the ischemic brain. Violation of the NINDS study protocol, particularly in the cases of delayed treatment after 3 h of stroke onset, high blood pressure, and the use of antithrombotic agents early after the treatment may cause an increase in patients with symptomatic intracranial hemorrhage and result in bad outcome.

The first Japanese guideline of stroke management published in 2004 recommends the use of intravenous rt-PA therapy (Grade A), and local proUK therapy (grade B), although both the therapy was not approved in Japan at the time of publication of the guideline [16].

4. Current status of acute stroke management in Japan

Several years ago, no clinical studies clarified the actual state of acute stroke management in Japan. To respond to these questions, the Japan Multicenter Stroke Investigators Collaboration (J-MUSIC) conducted a multicenter study from May 1999 to April 2000 (Chief Investigator: Takenori Yamaguchi). A total of 16,922 acute ischemic stroke patients admitted to 156 hospitals within the initial 7 days were consecutively registered [17,18]. Their mean age was 70.6 years old. The relative frequency of subtypes of ischemic stroke was 36% in lacunar, 31% in atherothrombotic and 20% in cardioembolic brain infarction. When compared with earlier data, the frequency of lacunar infarction was decreasing, atherothrombotic brain infarction was increasing, and cardioembolic brain infarction remained unchanged. Patients' age became older in the J-MUSIC than in older studies. When the outcome of patients at hospital discharge was compared among the ischemic stroke subtypes, patients with cardioembolic brain infarction had the worst outcome, associated to 19% in-hospital mortality and 45% in dependency.

In the J-MUSIC study, rt-PA was administered intravenously to only 0.3% of the patients registered. In contrast, intra-arterial rt-PA (0.5%) or urokinase (UK, 1.6%) therapy was done to 2.5% of the patients. A total of 91 patients with acute ischemic stroke admitted within the initial 4.5 h and having a NIHSS score greater than 4 but less than 23 on admission were treated with intra-arterial UK therapy. We compared the clinical outcome between these cases and 182 controls with similar clinical backgrounds but not treated with intravenous or intra-arterial thrombolytic therapy and found that good outcome as determined by the mRS score of 0–2 was significantly more frequent in the patients treated with intra-arterial UK than in the controls [19]. This case-control study strongly suggested the beneficial effects of hyperacute local UK thrombolytic therapy.

5. Clinical studies of thrombolytic therapy in Japan

The above-mentioned suggestion by the case-control study of the J-MUSIC has been tested with an RCT, the MCA-Embolism Local Fibrinolytic Intervention Trial Japan (MELT-Japan) chaired by Professor Ogawa. The detailed information of this study is available in the MELT-Japan homepage [http://melt.umin.ac.jp].

A phase III Japanese trial using open-label, single-dose alteplase for acute ischemic stroke was finished in 2004 (Japan Alteplase Clinical Trial, J-ACT) [20]. The study was designed to confirm the results of the alteplase group in the NINDS study. The study protocol was almost compatible with that of the NINDS study, except for several modifications. They included lower-dose administration of alteplase (0.6 mg/kg) in the J-ACT than that (0.9 mg/kg) in the NINDS study. Excluded were patients with pretreatment NIHSS score <5 and with coma, and those with the extent of early ischemic changes greater than 1/3 of the total MCA area. The number patients being studied was planned to be 100. Before the study began, the limits of primary endpoints were predetermined based on already published clinical data; patients with mRS score 0–1 at 3 months should be over 33.9% for the effectiveness and those with symptomatic ICH within 36 h post-treatment must be less than 9.6% for safety.

Although the internationally recommended dosage is 0.9 mg/kg, a 0.6 mg/kg dose was selected based on previous data for duteplase, an rt-PA very similar to alteplase. In a randomized double-blind trial carried out in Japan, 20 MIU of duteplase did not differ from 30 MIU in either recanalization rate or clinical improvement. However, massive brain hematoma or hemorrhagic transformation occurred only in 4% of patients given 20 MIU and 12% of those given 30 MIU [21]. Therefore, 0.6 mg/kg was selected for the present trial, which is equivalent to 20 MIU/60 kg of body weight, as the appropriate alteplase dose, instead of the 0.9 mg/kg in the NINDS trial. In addition, the optimal dose to attain a coronary patency rate of 65–80% was estimated at 0.5–0.75 mg/kg in Japan, which was much lower than the recommended dose in North America and EU [22].

The clinical backgrounds of J-ACT patients were almost similar to those in the NINDS study. Frequencies of very favourable outcome at 3 months and symptomatic intracranial hemorrhage were also comparable between the studies, indicating clinical efficacy and safety of intravenous alteplase therapy even for Japanese stroke patients [20].

6. The present and the future

Mainly based on the J-ACT data, the Japanese Government finally approved the use of intravenous alteplase therapy on October 11, 2005. Medical management of acute stroke patients will hopefully improve dramatically in Japan. New approaches other than intravenous alteplase monotherapy have been reported to reestablish blood flow in acute ischemic stroke. They include a combination of intravenous with intra-arterial thrombolysis, MR-based delayed thrombolysis up to 9 h after stroke onset, ultrasound-enhanced systemic thrombolysis, mechanical embolectomy, and combination therapy of thrombolytic agents with neuroprotective ones.

A great amount of investigative work will be needed to validate the potential of these therapeutic strategies. We appear to be on the threshold of an exciting new era for stroke management.

References

[1] K. Ueda, et al., Intracerebral hemorrhage in a Japanese community, Hisayama: incidence, changing pattern during long-term follow-up, and related factors, Stroke 19 (1988) 48–52.
[2] The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group, Tissue plasminogen activator for acute ischemic stroke, N. Engl. J. Med. 333 (1995) 1581–1587.
[3] W.-D. Heiss, G. Rosner, Functional recovery of cortical neurons as related to degree and duration of ischemia, Ann. Neurol. 14 (1983) 294–301.
[4] K. Minematsu, et al., Reversible focal ischemic injury demonstrated by diffusion-weighted magnetic resonance imaging in rats, Stroke 23 (1992) 1304–1311.
[5] K. Minematsu, T. Yamaguchi, T. Omae, 'Spectacular shrinking deficit': rapid recovery from a major hemispheric syndrome by migration of an embolus, Neurology 42 (1992) 157–162.
[6] E. Mori, et al., Intracarotid urokinase with thromboembolic occlusion of the middle cerebral artery, Stroke 19 (1988) 802–812.
[7] E. Mori, et al., Intravenous recombinant tissue plasminogen activator in acute carotid artery territory stroke, Neurology 42 (1992) 976–982.
[8] T. Yamaguchi, T. Hayakawa, H. Kikuchi, for the Japanese Thrombolysis Study Group, Intravenous tissue plasminogen activator ameliorates the outcome of hyperacute embolic stroke, Cerebrovasc. Dis. 3 (1993) 269–272.

[9] W. Hacke, et al., Intravenous thrombolysis with recombinant tissue plasminogen activator for acute hemispheric stroke. The European Cooperative Acute Stroke Study (ECASS), J.A.M.A. 274 (1995) 1017–1025.
[10] W. Hacke, et al., Randomised double-blind placebo-controlled trial of thrombolytic therapy with intravenous alteplase in acute ischemic stroke (ECASS II), Lancet 352 (1998) 1245–1251.
[11] W.M. Clark, et al., Recombinant tissue-type plasminogen activator (alteplase) for ischemic stroke 3 to 5 hours after symptom onset. The ATLANTIS Study: a randomized controlled trial. Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke, J.A.M.A. 282 (1999) 2019–2026.
[12] A. Furlan, et al., Intra-arterial prourokinase for acute ischemic stroke. The PROACT II Study: a randomized controlled trial, J.A.M.A. 282 (1999) 2003–2011.
[13] H.P. Adams Jr., et al., Guidelines for thrombolytic therapy for acute stroke: a supplement to the guidelines for the management of patients with acute ischemic stroke. A statement for healthcare professionals from a special writing group of the Stroke Council, American Heart Association, Stroke 27 (1996) 1711–1718.
[14] H. Adams, et al., Guidelines for the early management of patients with ischemic stroke. 2005 guidelines update. A scientific statement from the Stroke Council of the American Heart Association/American Stroke Association, Stroke 36 (2005) 916–921.
[15] The European Stroke Initiative Executive Committee and the EUSI Writing Committee, European Stroke Initiative recommendations for stroke management—update 2003, Cerebrovasc. Dis. 16 (2003) 311–337.
[16] Y. Shinohara, T. Yoshimoto, Y. Fukuuchi, et al. (Eds.), Japanese Guidelines for the Management of Stroke, Kyowa-kikaku, Tokyo, 2004 (in Japanese).
[17] K. Kimura, et al., Hospital-based prospective registration of acute ischemic stroke and transient ischemic attack in Japan, J. Stroke Cerebrovasc. Dis. 13 (2004) 1–11.
[18] K. Kimura, et al., Analysis of 16,922 patients with acute ischemic stroke and transient ischemic attack in Japan. A hospital-based prospective registration study, Cerebrovasc. Dis. 18 (2004) 47–56.
[19] T. Inoue, K. Kimura, K. Minematsu, A case-control analysis of intra-arterial urokinase thrombolysis in acute cardioembolic stroke, Cerebrovasc. Dis. 19 (2005) 225–228.
[20] K. Minematsu, et al., Results of clinical trial of intravenous rt-PA (alteplase) for acute ischemic stroke, Jpn. J. Stroke 26 (2004) 603–606 (in Japanese with English abstract).
[21] T. Yamaguchi, H. Kikuchi, T. Hayakawa, for the Japanese Thrombolysis Study Group, Clinical efficacy and safety of intravenous tissue plasminogen activator in acute embolic stroke: a randomized, double-blind, dose-comparison study of duteplase, in: T. Yamaguchi, E. Mori, K. Minematsu, et al. (Eds.), Thrombolytic Therapy in Acute Ischemic Stroke, vol. III, Springer-Verlag, Tokyo, 1995, pp. 223–229.
[22] S. Ueshima, O. Matsuo, The differences in thrombolytic effects of administered recombinant t-PA between Japanese and Caucasians, Thromb. Haemost. 87 (2002) 544–546.

＜症例報告＞

CTではなく，MRIで硬膜下血腫を診断しアルテプラーゼ静注療法を断念した1例

佐藤祥一郎　　髙田　達郎　　豊田　一則　　峰松　一夫

要旨：症例は104歳女性．突然の転倒と意識障害の発症後1時間45分で来院した．心原性脳塞栓症と診断し，アルテプラーゼ静注療法を検討したが，CTで同定し得なかった硬膜下血腫をMRIのFLAIR画像および拡散強調画像で診断した．超高齢であること，比較的広汎な早期虚血変化と併せて適応外と判断した．転倒や頭部打撲を伴った症例では，CTで検出できずMRI撮像が必要な外傷性頭蓋内出血もあることを念頭におくべきであろう．

Key words : cerebral infarction, subdural hematoma, thrombolytic therapy, tissue-type plasminogen activator

(脳卒中 28 : 408—410，2006)

はじめに

2005年10月，発症3時間以内の虚血性脳血管障害に対するアルテプラーゼ静注療法が承認された．日本脳卒中学会により適正治療指針が策定され[1]，安全かつ効果的な治療の実践が望まれている．

我々は，発症3時間以内の超急性期に来院した脳梗塞症例において，CTで検出不能であった硬膜下血腫をMRIで診断した．アルテプラーゼ静注療法の適応決定のためのMRI撮像の意義を考える上で，重要な症例と考えられたので報告する．

症　例

患者：104歳，女性，右利き．

主訴：呼びかけに返答がない．

既往歴・家族歴：特記事項なし．

現病歴：以前より高血圧あるも未治療であった．2005年某日夜，起立直後に突然倒れ，右顔面を打撲した．家人の呼びかけに返答しなかった．発症から105分後，救急車で当院に搬入された．

入院時一般身体所見：身長145cm，体重39.8kg，血圧162/76mmHg，脈拍100/分で不整，体温36.0℃．心尖部に最強点をもつLevine 3/6の収縮期心雑音を聴取した．頭頸部血管雑音なく，末梢動脈は触知良好であった．右頬部に皮下出血を認めた．

入院時神経学的所見：意識はJapan coma scale I-3，全失語，左共同偏倚，右中枢性顔面麻痺，弛緩性右片麻痺があり，深部腱反射は右上下肢で亢進し，右Babinski反射が陽性であった．National Institute of Health Stroke Scaleスコアは17であった．

入院時検査所見：血算は正常で，生化学検査ではLDH 252IU/l，CK 256IU/lと筋逸脱酵素の上昇あり，CRPは2.12mg/dlと上昇していた．凝固系では，TAT 5.55ng/ml，D-dimer 2.5μg/mlと中等度の上昇を認めた．検尿は正常であった．心電図で心房細動があり，胸部X線写真で軽度心拡大を認めた．

入院時頭部画像所見：発症2時間後の頭部CTでは，左頭頂葉に辺縁明瞭な低吸収域を認め，陳旧性梗塞と考えられた(Fig. 1A)．隣接する左中大脳動脈領域皮質の約1/3の範囲に皮髄境界の不鮮明化を認め，早期虚血所見を疑った．頭蓋内出血の所見は認めなかった．直後のMRI拡散強調画像では，CTで早期虚血所見を疑った部位に一致して高信号域を認めた（Fig. 1B）．左前頭から弁蓋部にかけての硬膜下に三日月状の高信号域を認め，硬膜下血腫に相当する所見であった（Fig. 1B）．FLAIR画像でも，同部は高信号を呈した(Fig. 1C)．MRAでは左中大脳動脈主幹遠位部以降が描出不良であった．

国立循環器病センター内科脳血管部門

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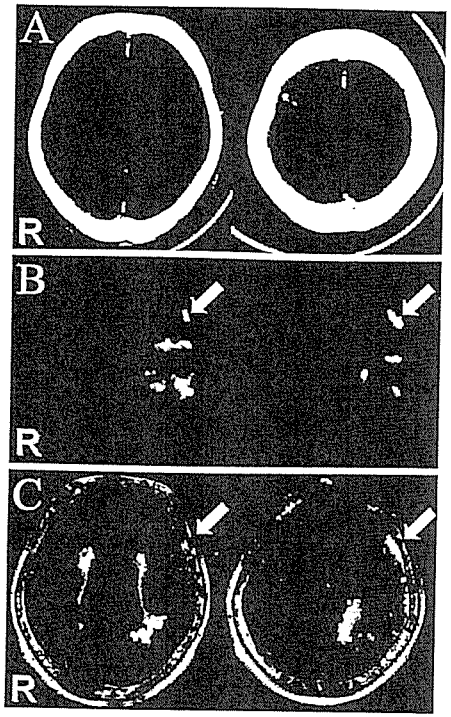

Fig. 1　A：頭部CT，B：頭部MRI（拡散強調画像），C：頭部MRI（FLAIR画像）
A：左中大脳動脈領域皮質の約1/3に皮髄境界の不鮮明化を認める．
B：左中大脳動脈領域に高信号域を認める．また，硬膜下に三日月状の高信号域を認める（矢印）．
C：硬膜下に高信号域を認める（矢印）．

入院後経過：心房細動を基礎疾患とする超急性期の心原性脳塞栓症と診断し，アルテプラーゼ静注療法の適応を検討した．超高齢であること，CTで広汎な早期虚血性変化を認めたこと，さらにMRIで硬膜下血腫と診断したことより，同療法を断念した．第2病日に左下肢皮膚の色調変化があり，左膝窩より遠位の動脈触知が不能となった．下肢動脈の超音波検査とCT動脈造影で左浅大腿動脈の閉塞を認め，急性動脈塞栓症と診断した．抗凝固療法を開始したが，家族の強い希望があり，近医に転院した．その後，消化管出血と肺炎を合併し，発症15日目に死亡した．

考　察

硬膜下血腫はCTで高吸収域を呈することが多いが，撮影時期によっては等～低吸収域を呈する場合もある[2]．本例の硬膜下血腫は極めて少量であり，かつ吸収値も高くなかったため，CT所見からその存在を診断することは困難であった．CTで等吸収を呈する硬膜下血腫と硬膜下水腫の鑑別には，MRIのFLAIR画像が有用といわれる[3]．また拡散強調画像における硬膜下の帯状高信号が比較的最近の血腫を示唆するという報告もある[4]．本例では，FLAIR，拡散強調画像とも頭蓋骨直下に高信号病変を呈していた．これは，発症時に転倒した際，回転加速度が加わることにより打撲側の対側の架橋静脈が破綻して生じた急性硬膜下血腫もしくは，慢性硬膜下血腫内に新たに生じた出血と考えられた．

血栓溶解療法の最大の合併症は，症候性頭蓋内出血である．急性心筋梗塞に血栓溶解療法を行ったGUSTO-1研究[5]では，登録症例の0.6%にあたる244例に症候性頭蓋内出血を合併した．その1/6は硬膜下血腫で，その存在は14日以内に先行する頭部外傷や2日以内に先行する失神と強く相関した．

日本脳卒中学会のアルテプラーゼ静注療法適正治療指針では，10日以内の外傷を有する例では適応を慎重に検討すること，頭蓋内出血の合併が明らかであれば「禁忌」と定めている[1]．一般に出血病変の診断にはCTがMRIより勝るとされている．しかしながら閉鎖性頭部外傷107例の検討によると，硬膜下および硬膜外血腫の診断感度は，CTが31%に対してMRIが97%と後者が有意に優れていた[6]．Packardら[7]は，一過性脳虚血発作を疑われた症例で，CTで分からなかった頭蓋内出血をMRIで診断し得たと報告し，血栓溶解療法時にCTのみで頭蓋内出血を除外することの危険性を指摘している．頭部打撲を伴うがCTで出血病変を認めなかった脳梗塞症例に経動脈的血栓溶解療法を実施し，治療後に急性硬膜下血腫を発症した報告もある[8]．このような例では，血栓溶解療法以前に外傷性血腫が存在した可能性がある．

アルテプラーゼ静注療法は，発症3時間以内に治療を開始しなければならず，その時間的制約は大きい．そのため，本治療を行うにあたってCT以外の画像診断を実施する意義は未だ確立していない．しかし，本例のように脳梗塞発症時や発症に先行して転倒や頭部

外傷を伴った場合には，CT で検出不能な出血の存在を念頭に置いて，時間の制限にも配慮しつつ MRI 撮像を加えることを勧めたい．

文　献

1) 日本脳卒中学会医療向上・社会保険委員会 rt-PA（アルテプラーゼ）静注療法指針部会：rt-PA（アルテプラーゼ）静注療法適正治療指針．脳卒中　27 : 327—354, 2005
2) 川又達朗，片山容一：慢性硬膜下血腫．太田富雄，松谷雅生（編）：脳神経外科学．第 9 版．京都，金芳堂，2004, pp 1165—1176
3) Ashikaga R, Araki Y, Ishida O : MRI of head injury using FLAIR. Neuroradiology 39 : 239—242, 1997
4) Kuwahara S, Fukuoka M, Koan Y, et al : Subdural hyperintense band on diffusion-weighted imaging of chronic subdural hematoma indicates bleeding from the outer membrane. Neurol Med Chir (Tokyo) 45 : 125—131, 2005
5) Gebel JM, Sila CA, Sloan MA, et al : Thrombolysis-related intracranial hemorrhage. A radiographic analysis of 244 cases from the GUSTO-1 trial with clinical correlation. Stroke 29 : 563—569, 1998
6) Orrison WW, Gentry LR, Stimac GK, et al : Blinded comparison of cranial CT and MR in closed head injury evaluation. AJNR Am J Neuroradiol 15 : 351—356, 1994
7) Packard AS, Kase CS, Aly AS, et al : "Computed tomography-negative" intracerebral hemorrhage. Case report and implications for management. Arch Neurol 60 : 1156—1159, 2003
8) Meguro T, Higashi H, Nishimoto K : Acute subdural hematoma after intra-arterial thrombolysis for acute ischemic stroke. —Case report—. Neurol Med Chir (Tokyo) 45 : 627—630, 2005

Abstract

CT-negative but MRI-positive subdural hematoma in hyperacute ischemic stroke

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A 104-year-old woman suddenly developed right hemiplegia and aphasia due to cardioembolic stroke. At onset, she fell down and bruised her face. Although computed tomography (CT) did not demonstrate apparent intracranial hemorrhage, diffusion-weighted and FLAIR magnetic resonance imaging (MRI) revealed a small amount of subdural hematoma. Accordingly, we did not use intravenous recombinant tissue-type plasminogen activator for her stroke. MRI appears to be more capable of detecting intracranial hemorrhage than does CT. For patients with hyperacute ischemic stroke who have a recent history of head injury, MRI may be advantageous over CT as a decisive diagnostic tool for indicating thrombolytic therapy.

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<原　著>

中大脳動脈塞栓症に対する局所線溶療法における経時的NIHSSおよびJSS評価の意義

髙田　達郎　　永野　恵子　　成冨　博章　　峰松　一夫

要旨：局所線溶療法（LIT）におけるNational Institute of Health stroke scale（NIHSS）とJapan Stroke Scale（JSS）の有用性を検討した．対象は中大脳動脈塞栓症16例で，LIT前，直後，24時間後および1カ月後にNIHSSとJSSを，退院時にmodified Rankin scale（mRS）およびBarthel index（BI）を評価した．各時期とも両スコアは有意に相関し，退院時BIは24時間後のJSSスコア，1カ月後の両スコアと相関した．退院時mRSは24時間後，1カ月後の両スコアと相関した．退院時自立（mRS≤2）に対するLIT直後のNIHSSスコア2以上およびJSSスコア0.65以上の改善での感度はそれぞれ0.75, 0.75, 特異度1.00, 0.875であった．LITにおいて経時的な脳卒中スケール評価は退院時転帰の予測に有用であった．

Key words : local intra-arterial thrombolysis, intravenous thrombolytic therapy, cerebrovascular disorders, Japan stroke scale, National Institute of Health stroke scale

（脳卒中 28 : 367—372，2006）

はじめに

脳卒中の重症度評価方法として，National Institute of Health stroke scale（NIHSS）が用いられている[1]．本邦ではNIHSSに加え，日本脳卒中学会により開発されたJapan Stroke Scale（JSS）も用いられている[2]．血栓溶解療法時には症候性頭蓋内出血とNIHSSスコアとの関連が指摘されており[3]，治療前のNIHSSによる評価は必須のものとなっている．しかし，血栓溶解療法後における脳卒中スケールの経時的評価と退院時転帰との関連，治療効果判定や退院時転帰の予測などに対する意義は十分には明らかとなっていない．今回，我々は中大脳動脈（middle cerebral artery，MCA）閉塞に対するウロキナーゼを用いた局所線溶療法（local intra-arterial thrombolysis，LIT）において経時的なNIHSS及びJSS評価を実施し，その臨床的意義について検討した．

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対象および方法

1．LITの適応基準

国立循環器病センター内科脳血管部門におけるLITの適応基準を示す．

1）発症6時間以内に治療開始可能であること，2）年齢は20～85歳，3）発症様式および臨床所見などから塞栓性機序が示唆されること，4）NIHSSスコアが5以上29以下であること，5）本人または患者家族からinformed concentを得られること，6）除外基準を満たさないこと，以上を治療適応例とした．除外基準としては，臨床上，1）脳腫瘍，感染性心内膜炎などの他の原因による血管閉塞でない，2）痙攣発作の合併がない，3）4週間以内の完成型脳卒中の既往がない，4）2週間以内の手術，生検，臓器損傷を伴う外傷および臓器出血の既往がない，5）4週間以内の重症頭部外傷の既往がない，6）血小板数は$10\times10^4/mm^3$未満でない，7）抗凝固療法中ではINRが1.7を超えない，8）治療抵抗性の高血圧を有さない（収縮期血圧＞185，拡張期血圧＞100），9）授乳中，妊娠またはその可能性がないこととした．CTでは，1）腫瘍，脳出血，くも膜下出血を認めない，2）新鮮梗塞およびそれによるmass ef-

fectがない，3）閉塞血管領域の33％以上の皮髄境界不鮮明化を認めないこととし，脳血管撮影検査では，1）内頸動脈閉塞ではない，2）脳底動脈本幹部全域にわたる閉塞ではない，3）2枝にわたる主幹動脈閉塞を認めない，4）血管解離を認めないこととした．

2．対象

国立循環器病センター内科脳血管部門では，この適応基準に基づき，1997年4月より2002年5月までに36例に対してLITを実施した．うち，MCA閉塞は27例であった．この27例のうち発症前modified Rankin scale（mRS）スコア≦2の条件を満たし，かつNIHSSおよびJSSを経時的に評価し得た16例を検討対象とした．

NIHSSおよびJSSは，LIT施行前，直後，24時間後および1カ月後に評価した．転帰判定のため，退院時にBarthel index（BI）およびmRSを評価した．

3．解析方法

a）各評価時において，1）NIHSSスコアとJSSスコア，2）NIHSSおよびJSSスコアと退院時BIスコア，3）NIHSSおよびJSSスコアと退院時mRSスコアとの相関関係を求めた．相関関係はSpearmanの相関係数で表し，$p<0.05$をもって有意な相関とした．b）LIT前のNIHSSスコアおよびJSSスコアよりLIT直後および24時間後の各スケールの点数を引いた値を∆NIHSS，∆JSSとし，転帰良好（退院時mRSスコア≦2）予測に対する感度，特異度，陽性反応適中度（positive predict value，PPV），陰性反応適中度（negative predict value，NPV）を求めた．c）左右半球病変別にLIT直後および24時間後の∆NIHSS，∆JSSの感度，特異度，PPV，NPVを求めた．

結　果

表1に患者背景を示す．年齢は，66±13歳，男性が12例（75％）であった．病型としては，心原性脳塞栓症が15例（94％）を占め，12例（75％）が心房細動を有していた．心室瘤，心房粗動，左室壁運動異常がそれぞれ1例であった．頸動脈狭窄によるartery to artery embolismを1例で認めた．7例（43.8％）はMCA主幹部（M1）閉塞で，その他はMCA分岐部（M2）閉塞であった．6例（37.5％）が左半球病変であった．危険因子としては，高血圧が56.2％，高コレステロール血症は12.5％であった．糖尿病は6.2％と低頻度であった．発症より来院までの時間は，0.93±0.96時間で，4例は院内発症であった．LIT開始までは3.6±1.23時間であった．治療前CTでは，68.8％に何らかの早期虚血変化（島回の消失，基底核構造の不鮮明化，MCA領域33％未満の皮髄境界不鮮明化）を認めた．治療前NIHSSスコアは中央値18（範囲：6～22），JSSスコアは16.28（1.69～25.48）であった．入院期間は39±11日で，退院時BIスコアは中央値75（0～100），8例（50％）で退院時mRSスコアが2以下となった．症候性頭蓋内出血および入院中の死亡はなかった．

表1　患者背景（16例）

年齢（平均±SD）	66±13歳
男性	75.0％
危険因子	
高血圧	56.2％
糖尿病	6.2％
高脂血症	12.5％
喫煙	18.8％
飲酒	42.3％
心房細動	75.0％
心原性脳塞栓症	94.0％
左半球病変	31.0％
中大脳動脈主幹部（M1）閉塞	43.8％
来院時NIHSSスコア	18（6～22）*
来院時JSSスコア	16.28（1.69～25.48）*
早期虚血変化	68.8％
抗凝固療法中	26.9％
抗血小板療法中	15.4％
発症からの時間	
来院時間	0.93±0.96時間
LIT開始時間	3.6±1.23時間
退院時BI	75（0～100）*
退院時mRS≦2	50.0％
症候性頭蓋内出血	0％
死亡率	0％
入院期間	39±11日

*中央値（範囲）

NIHSSスコアとJSSスコアは各時期とも有意な相関を示した（表2）．LIT前および直後のNIHSSスコアと退院時BIスコアに関連はなかった．LIT前，直後のNIHSSスコアとmRSスコアにも相関はなかった．LIT前後のJSSスコアもNIHSSと同様の結果であった．退院時BIスコアは治療24時間後のJSSスコアと有意な相関を示し，発症1カ月後のNIHSSおよびJSSスコアとも有意に相関した（表3）．退院時mRSスコアは治療24時間後および1カ月後のNIHSSスコア，JSSスコアと有意に相関した（表4）．

表2　各評価時におけるNIHSSスコアとJSSスコアの関連

	NIHSSスコア	JSSスコア	ρ	p値
LIT前	18（6～22）	16.28（1.69～25.48）	0.8151	0.0001
LIT直後	15（5～21）	15.7（2.18～25.55）	0.7733	0.0004
24時間後	14（2～20）	14.23（−0.52～23.63）	0.7965	0.0002
1カ月後	8（1～16）	4.54（−0.52～23.63）	0.8474	＜0.0001

中央値（範囲）
NIHSS：National Institute of Health stroke scale，JSS：Japan Stroke Scale

表3　各評価時におけるNIHSSおよびJSSスコアと退院時BIスコアの関連

	NIHSSスコア		JSSスコア	
	ρ	p値	ρ	p値
LIT前	0.0464	0.8645	−0.0123	0.9639
LIT直後	−0.4291	0.0972	−0.3721	0.1558
24時間後	−0.4860	0.0563	−0.5474	0.0282
1カ月後	−0.7645	＜0.0006	−0.7042	0.0023

NIHSS：National Institute of Health stroke scale，JSS：Japan Stroke Scale
BI：Barthel Index

表4　各評価時におけるNIHSSおよびJSSスコアと退院時mRSスコアの関連

	NIHSSスコア		JSSスコア	
	ρ	p値	ρ	p値
LIT前	−0.1447	0.5928	−0.0769	0.7770
LIT直後	0.4412	0.0872	0.2524	0.3457
24時間後	0.6413	0.0074	0.5463	0.0286
1カ月後	0.8279	＜0.0001	0.8033	0.0002

NIHSS：National Institute of Health stroke scale，JSS：Japan Stroke Scale
mRS：modified Rankin Scale

LIT直後の∆NIHSSが2以上ある場合，感度，特異度，PPV，NPVはそれぞれ0.75，1.00，1.00，0.80であった．一方，∆JSSでは0.65以上の場合，それぞれ0.75，0.875，0.875，0.778であった．治療24時間後の∆NIHSS≧4および∆JSS≧1.8での感度，特異度，PPV，NPVは，それぞれ0.75 vs. 0.875，0.875 vs. 0.875，0.75 vs. 0.875，0.778 vs. 0.875であった（表5）．左半球病変では，24時間後の感度，特異度が右半球病変に比較し低かった（表6）．

考　察

1995年，National Institute of Neurological Disorders and Stroke（NINDS）rt-PA Stroke Studyにおいて発症3時間以内の虚血性脳血管障害に対するrecombinant tissue plasminogen activator（rt-PA）静注法の有効性が示された[4]．その後，いくつかの臨床試験を経て，rt-PA静注療法は超急性期虚血性脳血管障害に対する治療法として確立した．本邦では，2002年にJapan Alteplase Clinical Trial（J-ACT）が開始され，海外の臨床成績と遜色ない結果となり，2005年10月に発症3時間以内の虚血性脳血管障害に対する治療として承認された[5]．一方，1999年に報告されたProlyse in Acute Cerebral Thromboembolism（PROACT）II studyによって，LITの有効性も示された[6]．これらの

表 5　退院時転帰良好（mRS ≤ 2）に対する感度，特異度，陽性反応適中度，陰性反応適中度

	感度	特異度	PPV	NPV
LIT 直後のスコア改善				
Δ NIHSS スコア≥ 2	0.750	1.00	1.00	0.800
Δ JSS スコア≥ 0.65	0.850	0.875	0.857	0.778
LIT24 時間後のスコア改善				
Δ NIHSS スコア≥ 4	0.750	0.875	0.750	0.778
Δ JSS スコア≥ 1.8	0.875	0.875	0.875	0.875

PPV：陽性反応適中度，NPV：陰性反応適中度

表 6　左および右半球における退院時転帰良好（mRS ≤ 2）に対する感度，特異度，陽性反応適中度，陰性反応適中度

	感度	特異度	PPV	NPV
LIT 直後Δ NIHSS スコア≥ 2				
右半球	0.60	1.00	1.00	0.714
左半球	1.00	1.00	1.00	1.00
LIT 直後Δ JSS スコア≥ 0.65				
右半球	0.80	0.80	0.80	0.80
左半球	0.67	1.00	1.00	0.75
LIT24 時間後Δ NIHSS スコア≥ 4				
右半球	1.00	1.00	1.00	1.00
左半球	0.333	0.333	0.50	0.50
LIT24 時間後Δ JSS スコア≥ 1.8				
右半球	1.00	1.00	1.00	1.00
左半球	0.667	0.667	0.667	0.667

PPV：陽性反応適中度，NPV：陰性反応適中度

臨床試験では重症度評価に NIHSS が用いられた．NIHSS は意識状態，視野，眼球運動，顔面神経麻痺，四肢筋力，失調，知覚，言語，半側空間無視からなる 15 項目の評価を行い，あらゆる脳血管障害の重症度評価に対応できるようにデザインされており，脳卒中発症より 3 カ月後の自立度との関連も示されている[1)7)]．前述の NINDS rt-PA Stroke Study の事後解析では，NIHSS スコアが 20 を超える重症例は症候性頭蓋内出血の危険因子の一つであることが指摘された[3)]．我々の検討では，NIHSS スコアの中央値は 18.5 例（31%）が 20 を超える重症例であったにも関わらず，症候性頭蓋内出血の発生はなかった．CT での広汎な早期虚血変化やその他の危険因子を厳格に除外したことが要因と考えられた．また，LIT 前 NIHSS スコアと退院時 mRS との関連は認められず，LIT の効果を反映したものと考えられた．

急性期虚血性脳血管障害における脳卒中スケールの役割には，臨床重症度の客観的な判定の他に治療効果の判定や転帰の予測が挙げられる．そのため，評価者間での信頼度，個々の評価者での再現性，臨床的な変動に相応した変化，専門的知識を要しない普遍的な評価技術などが要求される．NIHSS は，評価者間一致度は 0.69，再現性も 0.66〜0.77 と報告されており[1)]，非常に高い reliability を有している．また，看護師などの非神経内科専門医以外による評価においても reliability や validity が高いことが報告されている[8)]．Kasner ら[9)]は，急性期脳卒中 39 例に対して，6 人の評価者間での再現性を後ろ向きに検討した．評価者間一致度は 0.82 と非常に高い値を示し，後ろ向き研究での有用性も示された．しかし，本来 NIHSS の評価点数は他の脳卒中スケールと同様，便宜的につけられた根拠のない点数で，統計学的にはその順序にのみ意味をもつ順序尺度であり，総点の高い方がより重症度が高いことは示せるが，同じ点数の差が同様の重症度の差を示しているわけではない．一方，日本脳卒中学会によって考案された JSS は，この問題を解決するべく conjoint analysis の手法を取り入れ，各評価項目に重みづけを行い，定量的評価を可能にした世界初の脳卒中スケールである．Gotoh ら[2)]の検討では，評価者間での Weighted κ は 0.83，再現性も 0.998 と非常に高い reliability を有していた．今回の検討では，いずれの評価時期においても NIHSS と JSS との間には強い相関を認め，両脳卒中スケールの関連性も明らかとなった．

Wityk ら[10)]は急性期虚血性脳血管障害において，経時的な NIHSS 評価を行い，その変化は中大脳動脈塞栓症でより顕著であったことを報告した．JSS の経時的評価においても，すべての病型で症候の変化に則した点数の変化を認めた[2)]．しかし，血栓溶解療法における経時的脳卒中スケール評価の報告は少ない．Brott ら[11)]は，rt-PA 静注療法で経時的な NIHSS の評価を行い，治療 24 時間後の改善例のうち 53% は 2 時間後に著明改善していたことを示した．我々は中大脳動脈閉塞に対するウロキナーゼを用いた LIT において，治療直後の NIHSS スコアが治療前のそれより 2 以上改善することが退院時転帰良好（mRS≤2）の独立した予測因子であることを報告した[12)]．今回の検討でも退院時転帰良好に対する治療後 ΔNIHSS≥2 の感度は 75%，特異度は 100% であった．JSS では，ΔJSS≥0.65 で感度 75%，特異度 87.5% であった．いずれの評価スケールにおいても治療前後のスコア変化は退院時転帰予測に対して非常に高い感度，特異度を有しており，治療前後におけるこれらのスケール評価は転帰予測に有用であると考えられた．

NIHSS の各項目のうち，意識障害，運動麻痺，言語機能は総点数に占める割合が高く，より重視されている．Lyden ら[13)]は，rt-PA 静注法において，NIHSS の 15 項目のうち左半球症状，左運動障害，右半球症状，右運動障害の 4 つの因子と転帰との関連について報告した．一方で，Woo ら[14)]は，左右の半球梗塞体積と NIHSS スコアとの関係を検討した．同点数の NIHSS スコアでも，左半球梗塞体積は右半球梗塞のそれより小さく，NIHSS の点数配分の問題点が指摘された．JSS では，conjoint analysis による重みづけのため，感覚障害の素点がマイナス数値となっていること，意識障害に著しい重みづけがなされているにも関わらず，そのカテゴリーが 3 段階のみである点が問題として指摘されている[15)]．本研究でも，NIHSS，JSS ともに特異度に比較し，感度が低かった．治療直後から 24 時間後までの意識状態の改善は軽度の場合が多く，このことが点数の改善に反映されなかったと考えられた．もうひとつの問題として，今回の対象が MCA 塞栓症であったことより，高次脳機能障害の影響も無視できないことが挙げられる．NIHSS では言語機能は 42 点中 7 点を占めるの対して右半球機能である空間無視は 2 点を占めるのみである．JSS でも，意識障害および言語機能への重みづけがなされているにも関わらず，その点数カテゴリは 9 段階と少ない．表 6 に示した如く，退院時転帰良好に対する左右半球それぞれにおいて，治療前後に NIHSS スコア 2 以上，JSS スコア 0.65 以上の改善の感度・特異度には差はなかったが，治療 24 時間後に NIHSS スコア 4 以上，JSS スコア 1.8 以上の改善では左半球での感度・特異度が明らかに低かった．24 時間後までは，治療有効例においても意識障害や高次脳機能障害が残存していることが多いが，特に言語機能の障害が残存すると，障害の程度が軽度であっても点数の変化には反映されず，実際の症候の変化を十分に捉えきれなかった可能性がある．

LIT に限らず血栓溶解療法では，症候性頭蓋内出血対策などの後療法が転帰に影響しうる．そのため，治療直後〜24 時後において的確な治療効果判定がその後の迅速な対応に直結する．本研究により，脳卒中スケール評価は退院後の転帰を予測可能であり，血栓溶解療法後の治療方針決定に寄与することが示唆された．しかし，左半球症状を有する場合，軽微な変化を的確に捉えることが難しい可能性があり，その評価には注意を要する．

文　献

1) Brott T, Adams HP Jr, Olinger CP, et al : Measurements of acute cerebral infarction : a clinical examination scale. Stroke 20 : 864—70, 1989
2) Gotoh F, Terayama Y, Amano T : Development of a novel, weighted, quantifiable stroke scale : Japan stroke scale. Stroke 32 : 1800—7, 2001
3) The NINDS t-PA Stroke Study Group : Intracerebral hemorrhage after intravenous t-PA therapy for ischemic stroke. Stroke 28 : 2109—2118, 1997
4) The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group : Tissue plasminogen activator for acute ischemic stroke. N Engl J Med. 333 : 1581—1587, 1995
5) 山口武典，高田達郎，峰松一夫ら：rt-PA（アルテ

ブラーゼ）静注療法適正治療指針．脳卒中　27 : 327—354, 2005
6) Furlan A, Higashida R, Wechsler L, et al : Intra-arterial prourokinase for acute ischemic stroke. The PROACT II study : a randomized controlled trial. (Prolyse in Acute Cerebral Thromboembolism.) JAMA 282 : 2003—2011, 1999
7) Muir KW, Weir CJ, Murray GD, et al : Comparison of neurological scales and scoring systems for acute stroke prognosis. Stroke 27 : 1817—20, 1996
8) Goldstein LB, Samsa GP : Reliability of the National Institutes of Health Stroke Scale. Extension to non-neurologists in the context of a clinical trial. Stroke 28 : 307—10, 1997
9) Kasner SE, Chalela JA, Luciano JM, et al : Reliability and validity of estimating the NIH stroke scale score from medical records. Stroke 30 : 1534—7, 1999
10) Wityk RJ, Pessin MS, Kaplan RF, et al : Serial assessment of acute stroke using the NIH Stroke Scale. Stroke 25 : 362—5, 1994
11) Brott TG, Haley EC Jr, Levy DE, et al : Urgent therapy for stroke. Part I. Pilot study of tissue plasminogen activator administered within 90 minutes. Stroke 23 : 632—40, 1992
12) Takada T, Yasaka M, Minematsu K, et al : Predictors of clinical outcome in patients receiving local intra-arterial thrombolysis without subsequent symptomatic intracranial hemorrhage against acute middle cerebral artery occlusion. AJNR Am J Neuroradiol 25 : 1796—801, 2004
13) Lyden P, Lu M, Jackson C, et al : Underlying structure of the National Institutes of Health Stroke Scale : results of a factor analysis. Stroke 30 : 2347—54, 1999
14) Woo D, Broderick JP, Kothari RU, et al : Does the National Institutes of Health Stroke Scale favor left hemisphere strokes? Stroke 30 : 2355—9, 1999
15) 浜野　均，篠原幸人：Japan stroke scale (JSS) 使用上の問題点—内科の立場より—．脳卒中　21 : 408—412, 1999

Abstract

Clinical significance of stroke scales evaluated periodically in acute middle cerebral artery occlusion receiving local intra-arterial thrombolysis

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Background and Purpose : The neurological severity of acute ischemic stroke is evaluated worldwide using the National Institutes of Health stroke scale (NIHSS). In Japan, the Japan Stroke Scale (JSS) which was developed originally in Japan is also used. Several reports have suggested the efficacy of stroke scales for the evaluation of acute ischemic stroke receiving thrombolytic therapy. We assess the clinical usefulness of the NIHSS and JSS in cases receiving local intra-arterial thrombolysis (LIT). Methods : Neurological severity was assessed before, immediately after, and at 24 hours and one month after LIT using the NIHSS and JSS. We evaluated outcome at discharge based on the modified Rankin Scale (mRS) and the Barthel index (BI) score. Results : Sixteen patients receiving LIT underwent assessment by the NIHSS and the JSS. The NIHSS score was significantly related to the JSS score at each time of measucement. The mRS score at discharge was significantly related to both the stroke scale scores at 24 hours and those at one month after LIT. When the NIHSS score improved immediately by 2 or more after LIT and the JSS score improved by 0.65 or more, the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for a good outcome (mRS $\leq$ 2) at discharge were 0.75 vs. 0.75, 1.00 vs. 0.875, 1.00 vs. 0.875, and 0.80 vs. 0.778, respectively. Conclusion : Periodical evaluation of the NIHSS and JSS in patients with acute middle cerebral artery occlusion receiving LIT is useful for predicting patient outcome at discharge.

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Case Report

A Case of Chordoid Meningioma with Allelic Loss of 1p36

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ABSTRACT

The unbalanced translocation der(1)t(1 ; 3)(p12-13 ; q11) with losses of 1p12-13-pter and 3q11-pter has been reported in three cases of chordoid meningioma. Thus far, only a few attempts have been made to analyze this rare variant of meningioma cytogenetically. We report a case of chordoid meningioma in a 68-year-old man. He presented with a large mass in the midline of the base of the frontal skull without surrounding edema and had experienced poor vision with visual field defects and anosmia for 6 months. We investigated the meningioma with fluorescence in situ hybridization and found that the lesion was solid and well-delineated, with low signal intensity on T_1-weighted sequences and high signal intensity on T_2- and proton density-weighted sequences. The tumor showed marked enhancement following gadolinium administration. Histologic examination revealed a tumor composed of trabeculae of eosinophilic vacuolated cells embedded in a myxoid matrix with a focally typical meningiomatous pattern. Electron microscopy revealed intercellular desmosomal junctions and complex cytoplasmic interdigitation. Tumor cells were immunoreactive for vimentin, epithelial membrane antigen, the progesterone receptor, p27, p53, and the epidermal growth factor receptor. Cytogenetic analysis revealed the deletion of 1p36, but not of 1q25, the 3p telomere, the 3q telomere, 10q23, alpha satellite DNA of chromosome 10, the 14q telomere, 19p13, 19q13, 22q11.2, or 22q13. Chromosome 1p36 is a candidate recurrence-associated genomic region in chordoid meningioma. (Jikeikai Med J 2006 ; 53 : 37-44)

Key words : chordoid meningioma, meningioma, fluorescence in situ hybridization, pathology

INTRODUCTION

Chordoid meningioma, first reported in 1980 by Connors[1] and given its present name in 1988 by Kepes et al.[2], is a comparatively new subtype of meningioma. In their small series of young patients (6 to 19 years old), chordoid meningioma was associated with microcytic anemia or dysgammaglobulinemia (Castleman's syndrome) or both. Couce et al, however, have shown that chordoid meningioma occurs mostly in adults, lacks sex predilection, and has no systemic manifestations[3]. Although chordoid meningioma accounts for only 0.5% of all meningiomas, it has a high recurrence rate (42% in one series)[3]. On the basis of its clinical behavior, chordoid meningioma is classified as World Health Organization grade II[4].

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The present case study describes the cytogenetic analysis of a chordoid meningioma using fluorescence in situ hybridization (FISH) and illustrates its cytologic, histopathologic, ultrastructural, and immunohistochemical features.

CASE REPORT

A 68-year-old man complained of visual disturbances lasting 6 months and was referred to our unit after magnetic resonance (MR) revealed an intracranial mass lesion. Physical examination revealed visual acuity of 20/2000 in the left eye and 20/25 in the right eye, superior hemianopsia in the left eye, and anosmia. Results of hematologic examination, including hemoglobin and immunoglobulin, were normal. MR revealed a large, extrinsic mass (6×6×4 cm), extending superiorly to indent both frontal lobes, in the midline of the base of the frontal skull, without surrounding edema. The lesion was solid and well-delineated, with low signal intensity on T_1-weighted sequences and high signal intensity on T_2-weighted and proton density-weighted sequences. The lesion showed marked enhancement following gadolinium administration (Fig. 1). The tumor was supplied by the bilateral ethmoidal arteries and the left maxillary artery. No bone lesion was found.

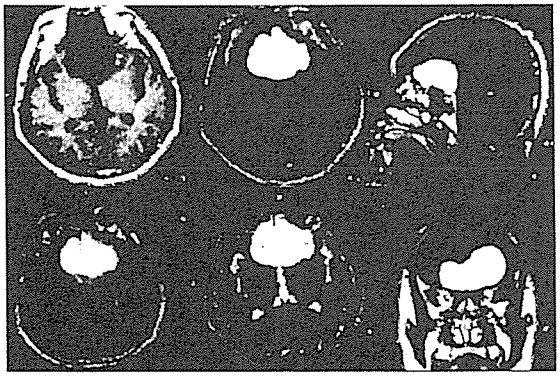

Fig. 1. Brain MR images
A large extrinsic mass (6×6×4 cm), extending superiorly to indent both frontal lobes, was located in the midline of the base of the frontal skull without surrounding edema. The lesion was solid and well-delineated, with low signal intensity on T_1-weighted sequences and high signal intensity on T_2- and proton density-weighted sequences. It showed marked enhancement following gadolinium administration.

The tumor was resected via a bilateral frontal and left frontotemporal approach. With the attachment on the dura of cribriform plate, a well-circumscribed, soft, tan-pink, gelatinous mass was debulked and excised (Simpson Grade II). The patient's postoperative course was uneventful, and visual acuity improved in both eyes. No radiation therapy was administered.

METHODS

Tumor tissue obtained at surgery was fixed in 10% buffered formalin and embedded in paraffin. Sections were stained with hematoxylin-eosin (H & E), periodic acid-Schiff (PAS), Alcian blue, and silver impregnation for reticulin fibers. Immunohistochemical studies were performed with monoclonal and polyclonal antibodies against vimentin, epithelial membrane antigen (EMA; E29; dilution 1:200; DAKO, Glostrup, Denmark), the progesterone receptor (PR; 1A6; dilution 1:800; Novocastra, Newcastle upon Tyne, UK), cytokeratin (CAM5.2; BD Biosciences, San Jose, CA, USA), S-100 (dilution 1:800; DAKO), glial fibrillary acidic protein (GFAP; dilution 1:3000; DAKO), carcinoembryonic antigen (CEA; II-7; dilution 1:50; DAKO), CD31 (JC/70A; dilution 1:50; DAKO), CD34 (My10; dilution 1:50; BD Biosciences), factor VIII (dilution 1:1000; DAKO), collagen type I (dilution 1:20; Southern Biotechnology Associates, Birmingham, AL, USA), collagen type II (dilution 1:20, Southern Biotechnology Associates), collagen type III (dilution 1:100, Southern Biotechnology Associates), collagen type IV, laminin (CIV22; dilution 1:100, DAKO), p53 (DO-7, dilution 1:50, Novocastra), p27 (1B4; dilution 1:20; Novocastra), bcl2 (124; dilution 1:40; DAKO), and the epidermal growth factor receptor (EGFR; EGFR.113; dilution 1:10; Novocastra). Ulex europeus agglutinin-1 (UEA1) lectin (E.Y. Laboratories, San Mateo, CA, USA) was also used for histochemical studies. The cell proliferative index was calculated according to the percentage of nuclei immunoreactive with the anti-human Ki-67 antibody (MIB-1; dilution 1:500; Zymed Laboratories, San Francisco, CA, USA) in 500 consecutive cells. FISH analysis was

performed with 1p36/1q25, the 3p telomere/3q telomere, PTEN (10q23)/CEP10, the 14q telomere, 19q13/19p13, and TUPLE1 (22q11.2)/ARSA (22q13) dual-color DNA probes (Vysis, Inc., Downers Grove, IL, USA). For each sample, 500 interphase nuclei were evaluated. (If more than 80% of the nuclei showed two green and two red signals, the case was regarded as "normal" ; one green or red signal was associated with deletion, and three green or red spots were regarded as duplication.) Specimens obtained from intraoperative touch smear cytology were stained with the Papanicolaou method. Several small fragments were also fixed with 3% glutaraldehyde and embedded in epoxy resin for ultrastructural study.

Pathological Findings

Microscopic examination showed that the tumor was composed of trabeculae of spindle-shaped and polygonal cells with an eosinophilic cytoplasm (Fig. 2d) and round or oval nuclei with a thin, smooth margin and delicate chromatin (Fig. 2f). Some cells had a physaliferous appearance. The tumor cells

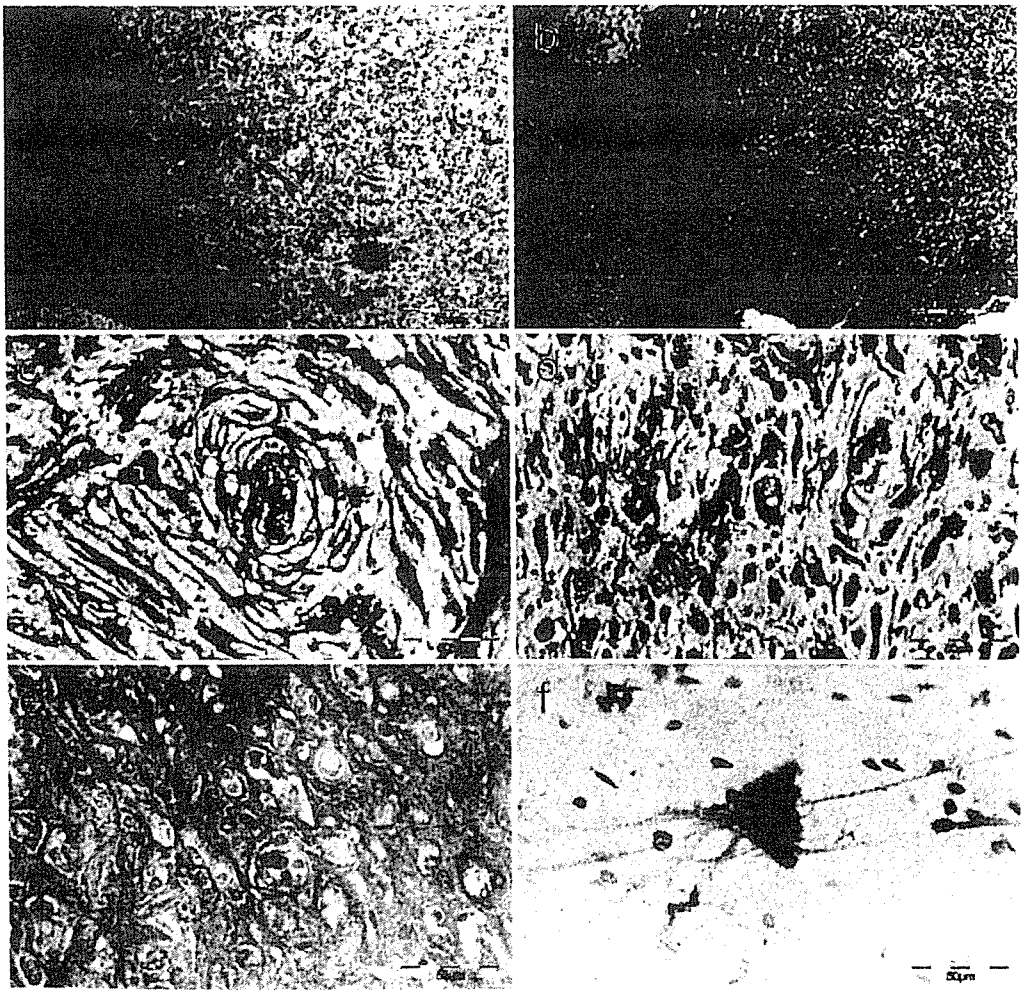

Fig. 2. Microscopic findings
(a) Cordlike arrangement of tumor cells embedded in abundant myxoid matrix (H & E). (b) A classic transitional meningioma pattern with lobular and fascicular arrangements merged at the borders (H & E). (c) Perivascular whorl formation (H & E). (d) Spindle-shaped and polygonal tumor cells with eosinophilic cytoplasm (H & E). (e) Alcian blue-positive mucinous matrices among the tumor cells. (f) Adhesive pseudosyncytial plates composed of medium-sized cells with indistinct cytoplasmic borders on touch smear cytology (Papanicolaou stain)

were embedded in an abundant myxoid matrix, which was basophilic on H & E staining (Fig. 2a), pink with the PAS reaction, and bright blue on Alcian blue staining at pH 2 (Fig. 2e), which is the histochemical pattern of acid mucin. Cytoplasmic vacuolization also exhibited the same staining pattern of the myxoid matrix. There were many small, adhesive pseudosyncytial plates composed of medium-sized cells with indistinct cytoplasmic borders in touch smear cytology (Fig. 2f). Whorl formation (Fig. 2c) and calcification were evident in some areas. No sizable lymphoplasmocytic infiltrate was found. In less than 3% of tumor specimens, a classic transitional meningioma pattern with lobular and fascicular arrangements merging at the borders with very extensive chordoid areas was observed (Fig. 2b).

Ultrastructural study demonstrated cohesive, often polygonal cells, featuring uniform, round-to-oval nuclei with delicate chromatin, as well as moderate quantities of cytoplasm containing abundant rough endoplasmic reticulum, mitochondria, and intermediate filaments. Basement membranes surrounding the cytoplasmic membrane were observed in some areas. Intercellular desmosomal junctions and complex cytoplasmic interdigitation were seen (Fig. 3). Weibel-Palade bodies were not observed.

Immunohistochemical studies of the surgically resected specimen showed strong, diffuse positivity for vimentin (Fig. 4a), EMA (Fig. 4b), PR (Fig. 4c), and p27 (Fig. 4g) in areas with the chordoid and classic patterns. Some tumor cells expressed p53 (Fig. 4e) and EGFR (Fig. 4f). However, staining was consistently negative for CAM5.2 (Fig. 4d), S-100, GFAP, CEA, CD31, CD34, factor VIII, collagen type I, collagen type II, collagen type III, collagen type IV, laminin, and bcl2. The MIB1 positivity rate (Fig. 4h) was 7% to 14% (mean, 10%).

Cytogenetic analysis revealed the deletion of 1p36, but not of 1q25, the 3p telomere, the 3q telomere, 10q23, alpha satellite DNA of chromosome 10, the 14q telomere, 19p13, 19q13, 22q11.2, or 22q13 (Fig. 5).

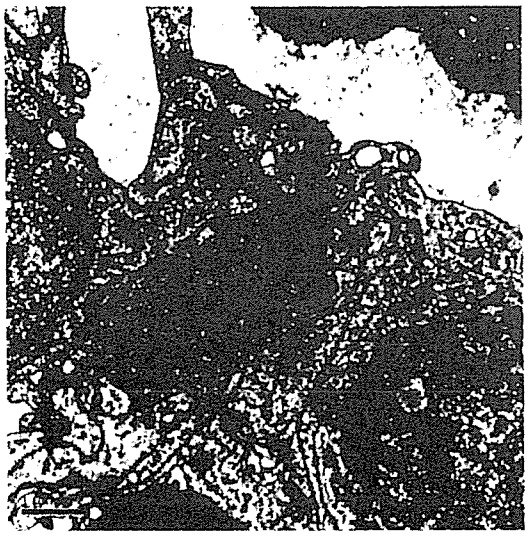

Fig. 3. Electron microscopic findings
Intercellular desmosomal junctions and complex cytoplasmic interdigitation were seen.

DISCUSSION

Most chordoid meningiomas (88%) are large and supratentorial[3]. The frontoparietal convexities and the parasagittal and falcotentorial regions are common sites of origin[2,3,5]. A large hypointense-to-isointense, dural-based, uniformly enhancing mass and moderate-to-marked adjacent white matter edema are common features on T_1-weighted MR sequences[5,9]. As in the present report, two previous reports have described chordoid meningiomas as showing high signal intensity in T_2-weighted sequences[5,6]. Although the authors of these reports have speculated high-intensity intralesional signals reflect, in part, lymphoplasmacytic infiltration, this is not a plausible explanation in the present case.

Cytologic touch smears are a highly reliable diagnostic method for chordoid meningioma[10,11] and show a pattern of abundant, closely knit plates inside which cellular limits are not visible, with some solitary, rounded cells. Nuclei are homogeneous and display a delicate chromatin pattern with a few conspicuous nucleoli and occasional intranuclear inclusions. The background is a fairly abundant, metachromatic, mucofibrillar matrix that does not appear between the cells inside the plates. Histologic studies show clustering or cords of eosinophilic, vacuolated (chordoid) cells in a myxoid matrix; thus, the histologic appearance of chordoid meningioma may mimic that of chordoma. Typical physaliphorous

tumor cells, however, are absent in chordoid meningiomas. Mucin-rich chordoid elements occupy 10% to 100% of the tumor area[3]. Periumoral and intratumoral lymphoplasmacellular infiltrates, often showing follicles and germinal centers with a predominance of T-lymphocytes over B-cells, may be prominent in some cases of chordoid meningiomas, particularly those in young patients, and may cause systemic manifestations of Castleman's syndrome[2]. Ultrastructurally, meningiomas have intercellular des-

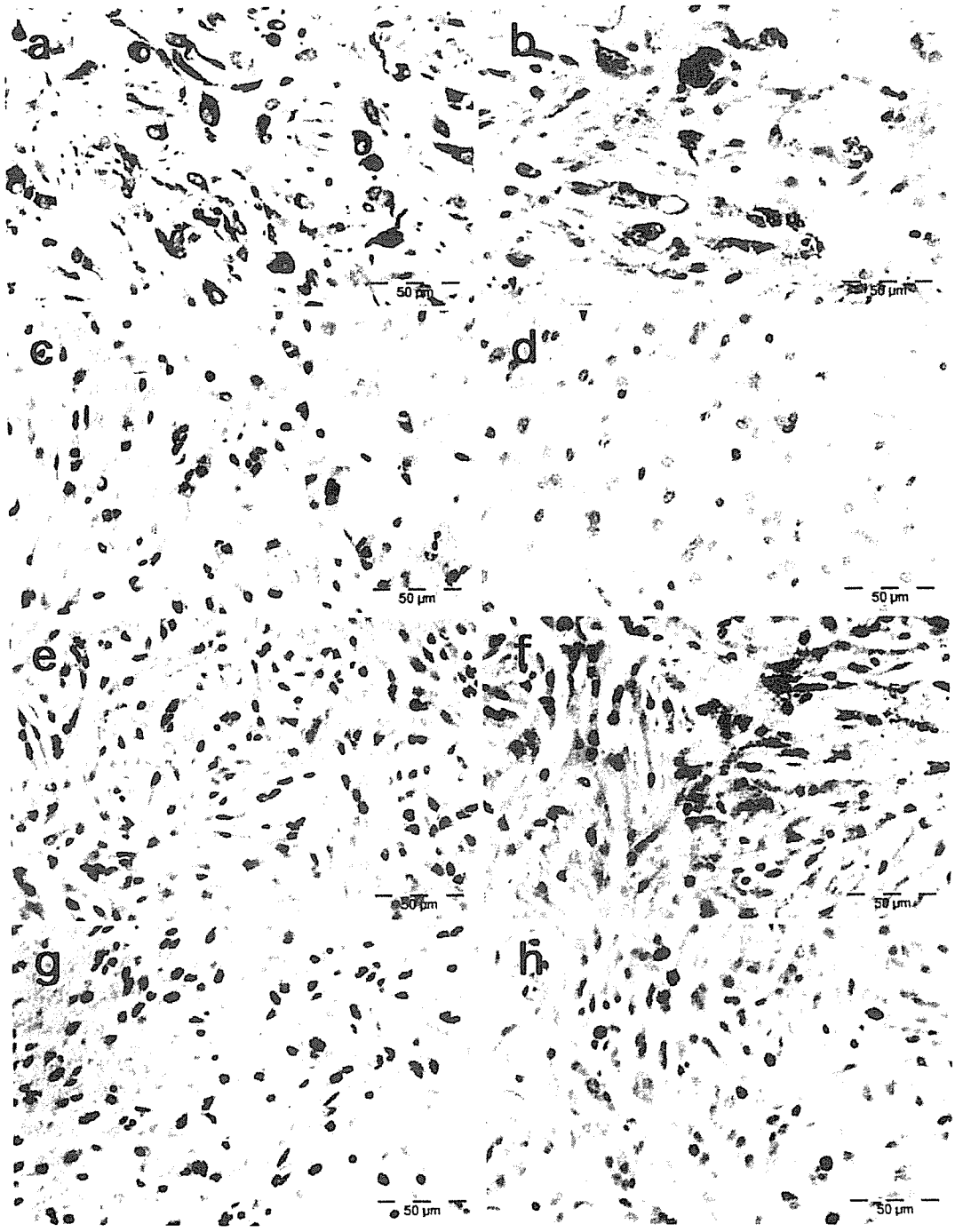

Fig. 4. Immunohistochemical findings
Positive cytoplasmic staining for vimentin (a) and EGFR (f). Positive membranous staining for EMA (b). Positive nuclear staining for PR (c), p53 (e), p27 (g), and MIB1 (h). Negative staining for CAM5.2 (d).

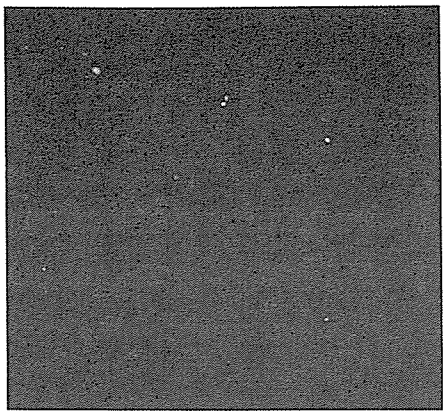

Fig. 5. FISH analysis
Tumor cells showing the deletion of 1p36 (orange) and a normal number of 1q25 (green).

mosomal junctions, intermediate filaments, and complex interdigitating cell processes, which at times may be difficult to appreciate in the chordoid variant[5]. Almost all tumor cells exhibit positive immunostaining for vimentin, EMA, and PR, but are negative staining for GFAP, S100, cytokeratins, CD34, CD57 (Leu7), and CEA[3,10,12]. Immunostaining for vimentin and EMA in the absence of prominent cytokeratin expression facilitates the differential diagnosis. In meningioma, MIB1 labeling indices higher than 5% to 10% suggest a greater likelihood of recurrence[4].

Microscopically, chordoma[13], chondroid chordoma[14], myxoid chondrosarocoma (chordoid sarcoma)[15,16], epithelioid hemangioendothelioma[17], metastatic mucinous carcinoma[18], and chordoid glioma[19] require immunohistochemical and ultrastructural examinations for their differentiation. The present case showed some chordoma-like features with lobules of vacuolated cells and physaliferous-like cells in a myxoid stroma. There were, however, small meningothelial elements in other parts of the tumor that aided the diagnosis of chordoid meningioma. This diagnosis was further supported by the immunoreactivity for vimentin, EMA, and PR and the ultrastructural findings of cytoplasmic interdigitations, desmosomes, and intermediate filaments, which are characteristic of meningioma. Immunohistochemically, chordomas are characterized by S-100 protein and cytokeratins[13], chondroid chordoma by S-100 protein[14], myxoid chondrosarcoma by cytoplasmic positivity for vimentin, synaptophysin, S-100, and EMA15, epithelioid hemangioendothelioma by CD31, CD34, factor VIII, and *Ulex europeus* lectin[17], metastatic mucinous carcinoma by cytokeratin[18], and chordoid glioma by GFAP19.

A large study of meningiomas has revealed that overexpression of p53 protein correlates with the MIB-1 proliferative index[20], histologic malignancy[21], and recurrence[22]. In another study, however, no relationship between p53 expression and prognosis was found[23]. Suggested roles of nuclear protein p21, a universal cyclin-dependent kinase inhibitor, also differ between studies. Amatya et al. have reported a negative correlation of the proliferative index with the histological grade of meningioma[24]. On the other hand, Korshunov et al. have found no correlation of p27 with various histologic and clinical outcomes[25]. EGFR seems to be highly expressed in meningiomas, but its clinical significance has not been established[26]. Thus, the roles of p53, EGFR, and p21 in meningiomas, especially chordoid meningioma, remain unclear.

Unbalanced translocation der(1)t(1 ; 3)(p12-13 ; q11) with losses of 1p12-13-pter and 3q11-pter has been reported in three cases of this rare variant meningioma by using chromosome microdissection and reverse FISH[27]. In this case, FISH analysis revealed deletion of 1p36, but not of 1q25, the 3p telomere, the 3q telomere, 10q23, alpha satellite DNA of chromosome 10, the 14q telomere, 19p13, 19q13, 22q11.2, or 22q13. Deletion of 1p, mainly in the regions 1p36, 1p35-p32, and 1p22-p13, is the most frequent progression-associated chromosomal aberration in meningiomas and is strongly correlated with tumor recurrence[28,30]. The results of the present case and previously reported cases[27,31] indicate that chromosome 1p36 is a candidate recurrence-associated genomic region in chordoid meningioma. Atypical and anaplastic meningiomas often show allelic losses of chromosomal arms 1p, 6q, 9q, 10q, 14q, 17p, and 18q and gains of 1q, 9q, 12q, 15q, 17q, and 20q, suggesting the presence of progression-associated genes at these loci[32,33]. Thus far, only a few attempts have been made to analyze chordoid meningioma cytogenetically. Therefore, further studies are required to demonstrate the clear significance of genetic factors for meningioma biology and clinical outcome.

References

1. Connors MH. Growth and maturation arrest, hypochromic anemia and hyperglobulinemia associated with a brain tumor. West J Med 1980 : 133 ; 160-3.
2. Kepes JJ, Chen WY, Connors MH, Vogel FS. "Chordoid" meningeal tumors in young individuals with peritumoral lymphoplasmacellular infiltrates causing systemic manifestations of the Castleman syndrome : a report of seven cases. Cancer 1988 : 62 ; 391-406.
3. Couce ME, Aker FV, Scheithauer BW. Chordoid meningioma : a clinicopathologic study of 42 cases. Am J Surg Pathol 2000 : 24 ; 899-905.
4. Louis DN, Scheithauer BW, Budka H, von Deimling A, Kepes JJ. 2000. Meningiomas. In : Kleihues P and Cavenee WK editors. Pathology and genetics of tumors of the nervous system. Lyon : IARC Press ; 2000. p. 176-84.
5. Kobata H, Kondo A, Iwasaki K, Kusaka H, Ito H, Sawada S. Chordoid meningioma in a child : case report. J Neurosurg 1998 : 88 ; 319-23.
6. Glasier CM, Husain MM, Chadduck W, Boop FA. Meningiomas in children : MR and histopathologic findings. AJNR Am J Neuroradiol 1993 : 14 ; 237-41.
7. Civit T, Baylac F, Taillandier L, Auque J, Hepner H. Chordoid meningiomas. Clinical, neuroradiological and anatomopathological aspects. Apropos of a new case and review of the literature. Neurochirurgie 1997 : 43 ; 308-13.
8. Kajiwara Y, Kodama Y, Hotta T, Kohno H, Taniguchi E, Yamasaki F, et al. A case of chordoid meningioma. No Shinkei Geka 1999 : 27 ; 947-51.
9. Soo MY, Ng T, Gomes L, Da Cruz M, Dexter M. Skull base chordoid meningioma : imaging features and pathology. Australas Radiol 2004 : 48 ; 233-6.
10. Salinero E, Beltran L, Costa JR. Intraoperative cytologic diagnosis of chordoid meningioma : a case report. Acta Cytol 2004 : 48 ; 259-63.
11. Inagawa H, Ishizawa K, Shimada S, Shimada T, Nishikawa R, Matsutani M, et al. Cytologic features of chordoid meningioma : a case report. Acta Cytol 2004 : 48 ; 397-401.
12. Zuppan CW, Liwnicz BH, Weeks DA. Meningioma with chordoid features. Ultrastruct Pathol 1994 : 18 ; 29-32.
13. Abenoza P, Sibley RK. Chordoma : an immunohistologic study. Hum Pathol 1986 : 17 ; 744-7.
14. Mierau GW, Weeks DA. Chondroid chordoma. Ultrastruct Pathol 1987 : 11 ; 731-7.
15. Cybulski GR, Russell EJ, D'Angelo CM, Bailey OT. Falcine chondrosarcoma : case report and literature review. Neurosurgery 1985 : 16 ; 412-5.
16. Martin RF, Melnick PJ, Warner NE, Terry R, Bullock WK, Schwinn CP. Chordoid sarcoma. Am J Clin Pathol 1973 : 59 ; 623-35.
17. Nora FE, Scheithauer BW. Primary epithelioid hemangioendothelioma of the brain. Am J Surg Pathol 1996 : 20 ; 707-14.
18. Radner H, Katenkamp D, Reifenberger G, Deckert M, Pietsch T, Wiestler OD. New developments in the pathology of skull base tumors. Virchows Arch 2001 : 438 ; 321-35.
19. Brat DJ, Scheithauer BW, Staugaitis SM, Cortez SC, Brecher K, Burger PC. Third ventricular chordoid glioma : a distinct clinicopathologic entity. J Neuropathol Exp Neurol 1998 : 57 ; 283-90.
20. Karamitopoulou E, Perentes E, Tolnay M, Probst A. Prognostic significance of MIB-1, p53, and bcl-2 immunoreactivity in meningiomas. Hum Pathol 1998 : 29 ; 140-5.
21. Aguiar PH, Agner C, Simm R, Freitas AB, Tsanaclis AM, Plese P. p53 Protein expression in meningiomas : a clinicopathologic study of 55 patients. Neurosurg Rev 2002 : 25 ; 252-7.
22. Matsuno A, Nagashima T, Matsuura R, Tanaka H, Hirakawa M, Murakami M, et al. Correlation between MIB-1 staining index and the immunoreactivity of p53 protein in recurrent and non-recurrent meningiomas. Am J Clin Pathol 1996 : 106 ; 776-81.
23. Perry A, Stafford SL, Scheithauer BW, Suman VJ, Lohse CM. The prognostic significance of MIB-1, p53, and DNA flow cytometry in completely resected primary meningiomas. Cancer 1998 : 82 ; 2262-9.
24. Amatya VJ, Takeshima Y, Sugiyama K, Kurisu, K. Nishisaka T, Fukuhara T, et al. Immunohistochemical study of Ki-67 (MIB-1), p53 protein, p21WAF1, and p27KIP1 expression in benign, atypical, and anaplastic meningiomas. Hum Pathol 2001 : 32 ; 970-5.
25. Korshunov A, Shishkina L, Golanov A. Immunohistochemical analysis of p16INK4a, p14ARF, p18INK4c, p21CIP1, p27KIP1 and p73 expression in 271 meningiomas correlation with tumor grade and clinical outcome. Int J Cancer 2003 : 104 ; 728-34.
26. Andersson U, Guo D, Malmer B, Bergenheim AT, Brannstrom T, Hedman H, et al. Epidermal growth factor receptor family (EGFR, ErbB2-4) in gliomas and meningiomas. Acta Neuropathol (Berl) 2004 : 108 ; 135-42.
27. Steilen-Gimbel H, Niedermayer I, Feiden W, Freiler A, Steudel WI, Zang KD, et al. Unbalanced translocation t(1 ; 3)(p12-13 ; q11) in meningiomas as the unique feature of chordoid differentiation. Genes Chromosomes Cancer 1999 : 26 ; 270-2.
28. Leone PE, Bello MJ, de Campos JM, Vaquero J, Sarasa JL, Pestana A, et al. NF2 gene mutations and allelic status of 1p, 14q and 22q in sporadic meningiomas. Oncogene 1999 : 18 ; 2231-9.
29. Bostrom J, Muhlbauer A, Reifenberger G. Deletion mapping of the short arm of chromosome 1 identifies a common region of deletion distal to D1S496 in human meningiomas. Acta Neuropathol (Berl) 1997 : 94 ; 479-85.
30. Bello MJ, de Campos JM, Kusak ME, Vaquero J, Sarasa